Pharmacological interventions against myocardial ischaemia and reperfusion injury

Akademisk avhandling

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av

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Professor Guro Valen
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The thesis is based on the following papers,

I Karlsson LO, Zhou AX, Larsson E, Åström-Olsson K, Akyürek LM, Grip L. Cyclosporine does not reduce myocardial infarct size in a porcine ischemia-reperfusion model. *J Cardiovasc Pharmacol Ther 2010 Jun; 15(2): 182-9*

II Karlsson LO, Bergh N, Grip L**.** Cyclosporine A, 2,5 mg/kg, does not reduce myocardial infarct size in a porcine model of ischemia and reperfusion *J Cardiovasc Pharmacol Ther 2011 Maj 13. (Epub ahead of print)*

III Karlsson LO, Grip L, Bissessar E, Bobrova I, Gustafsson T, Kavianpour M, Odenstedt J, Wikström G, Gonon AT. Opioid receptor agonist Eribis peptide 94 reduces infarct size in different porcine models for myocardial ischemia and reperfusion *Eur J Pharmacol. 2011 Jan 25;651(1-3): 146-51*

IV Karlsson LO, Bergh N, Li L, Bissessar E, Bobrova I, Gross GJ, Akyürek LM, Grip L**.** Dose-dependent cardioprotection of enkephalin analogue Eribis peptide 94 and cardiac expression of opioid receptors in a porcine model of ischaemia and reperfusion *Submitted*

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Pharmacological interventions against myocardial ischaemia and reperfusion injury

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ABSTRACT

Background: Ischaemic heart disease is the leading cause of death in the industrialised world. Although the concept of early restoration of coronary blood-flow constitutes an important factor to reduce the injury caused by myocardial ischaemia, reperfusion in itself can aggravate the damage to myocardial tissue, a phenomenon denoted myocardial reperfusion injury. Even though promising cardioprotective strategies have been presented in the pre-clinical setting, experience from the clinic has been largely disappointing.

Aims: To investigate whether two different pharmacological interventions, cyclosporine A (CsA) and the novel enkephalin analogue EP 94, could reduce myocardial infarct size in different porcine models of myocardial ischaemia and reperfusion. Furthermore, to examine the distribution of the opioid receptor subtypes in the porcine heart, and to investigate how this expression is affected by ischaemia and reperfusion.

Methods: Anesthetised pigs underwent balloon occlusion of the left anterior descending coronary artery, followed by reperfusion. CsA and EP 94 were administered during the end of the ischaemic insult. After the reperfusion period hearts were stained with Evans blue and 2, 3, 5-triphenyltetrazolium chloride to quantify area at risk and infarct size, respectively. mRNA and protein expression of different pro-apoptotic proteins, endothelial NO-synthetase and opioid receptor subtypes was quantified in the control and ischaemic/reperfused areas.

Results: Two different dosages of CsA did not confer cardioprotection whereas EP 94 reduced myocardial infarct size in a dose-dependant manner in our different porcine models. Immunoblots revealed a possible mechanism for the cardioprotective effect with up-regulation of phosphorylated eNOS in pigs receiving EP 94. Furthermore, protein expression of the κ- and δ-opioid receptors was detected in the left ventricle, with an up-regulation of the δ subtype after ischemia and reperfusion. The μ-opioid receptor was not detected.

Conclusions: CsA did not reduce myocardial infarct size, whereas the novel enkephalin analogue EP 94 conferred cardioprotection in different porcine models. The κ- and δ-opioid receptors were detected in the pig left ventricle.

Keywords: myocardial ischemia, reperfusion injury, opioids, cyclosporine A

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